REMARKS

Claims 1, 2, 4-19, 44-45, and 50-51 were pending in the present application. By this Amendment, Applicants have amended claim 1 by introducing the subject matter of claim 50 therein. Claim 50 has consequently been canceled without prejudice to the right to pursue any canceled subject matter in a future continuing application. Applicants have amended claims 2, 4, and 51 for clarity. Applicants also have added new claims 52-55. Support for the new claims can be found throughout the specification and claims as originally filed. Specifically, support can be found, *inter alia*, at paragraphs [0040] to [0056] of the specification. The present Amendment does not introduce any new matter and thus, its entry is respectfully requested. Upon entry of the present Amendment, claims 1-2, 4-5, 12-19, 44-45, and 51-55 will be pending and under examination. Applicants believe all of these claims are in allowable condition.

The November 2, 2007 Office Action

Examiner's comments on Applicants' previous response

In the Office Action, the Examiner, referring to a previous §103 rejection that had been withdrawn, stated the following:

> The 103 rejection was based on well-established case law, which states that a stereoisomer is not patentable over its known racemic mixture unless it possesses unexpected properties. (See In re Anthony, 162 USPQ 594, 596 (1969) and In re Adamson, 125 USPQ 233, 234 (1960)). Applicant argued that the equol in the prior art was not racemic and thus the case law did not apply.

> Examiner withdrew the 103 based on the assumption that the equol of the prior art was not racemic, but in reviewing the case history and state of the art, it appears that withdrawal of the 103 rejection was incorrect because the prior art equol could have been racemic. In addition, to the racemic issue, another issue is raised in terms of what the state of the art was at the time Applicants filed the instant claims. Prior art shows that the synthesis of s-equol was well known at the time and even available commercially. This action is to clarify the record.

In response, while Applicants do not agree with the Examiner's conclusions, and do not necessarily believe the statement accurately or fully characterizes the Applicants' previous replies, Applicants do appreciate the Examiner's efforts to summarize the reasoning behind her recent decisions. Applicants reiterate their position that the Examiner's earlier acknowledgment of allowable subject was proper and should not have been reversed. Moreover, Applicants now assert that the Examiner's above statement that "[p]rior art shows that the synthesis of s-equol was well known at the time and even available commercially," is not supported by the record. In any event, Applicants address the new claim rejections in full below.

Examiner's rejections under 35 U.S.C. §103

The Examiner rejected claims 1, 2, 4, 5, 12-19, 44, 45, 50, and 51, as allegedly obvious under 35 U.S.C. §103, over a single reference, Kelly, et al., U.S. Pat. 6,455,032 (already of record in the case). The Examiner's full rationale for the rejection is set forth at pages 3-5 of the Office Action. Applicants note that while the Examiner has referred to various references, the Examiner appears to be basing her rejection on Kelly, concluding that Applicants' claims to compositions consisting essentially of the S-enantiomer of equol are not patentable over Kelly's

teaching of compositions of racemic equol, absent a showing of unexpected properties of the stereoisomer. In particular, Applicants note the following statement by the Examiner: "A stereoisomer is not patentable over its known racemic mixture unless it possesses unexpected properties not possessed by the racemic mixture. In re Anthony, 162 USPQ 594, 596 (1969) and In re Adamson, 125 USPQ 233, 234 (1960)."

In response, Applicants initially note that the claims have been amended for clarity and to further advance prosecution of the application to allowance. To the extent the Examiner's present rejection can be applied to the amended claims, Applicants traverse. First, Applicants respectfully take issue with at least some of the statements made by the Examiner concerning the Kelly art and the other references noted. Applicants respectfully note that Kelly does not disclose enantiomers of equol. Moreover, the Examiner refers to several references that Applicants have no reason to believe are available as prior art against the present application. For example, the Examiner stated that "(R,S)-Equol is commercially available from LC Laboratories and US Biological." However, the Examiner has not shown that either of the references purported to support this statement was in fact published or in any way publicly available before the priority date of the present application.

In any event, Applicants believe the comments presented below, and the accompanying evidence of unexpected biological properties of S-equol over racemic equol, fully overcome the Examiner's rejections, and that the present claims, as amended, are in condition for allowance.

At the outset, Applicants note that the Examiner has not provided any art (including the

art referred to in the Office Action in addition to Kelly) showing or suggesting any composition as presently claimed. Rather, the Examiner's obviousness position appears to be based on the assumption that because racemic equol (as referred to in Kelly) can be useful, one of ordinary skill in the art would have been motivated to obtain the individual equol enantiomers for use in compositions (such as those claimed herein), with the presumption that biological activity typically resides in one such enantiomer. In that regard, the caselaw to which the Examiner refers further reflects the common presumption that the activity of one enantiomer will be twice that of the racemate, owing to the belief that the other enantiomer is inactive. Under this rationale, one of ordinary skill in the art would have been led to expect that if a racemic equol mixture is active, the activity can be attributed to the fact that one of the enantiomers, i.e., either the S-, or the R-, is solely responsible for the activity. A showing of unexpected properties of enantiomeric equol over the cited art's teachings of racemic equol therefore would be sufficient to overcome the obviousness rejection.

Accordingly, in an effort to expedite allowance of the subject application, Applicants now provide, as requested by the Examiner, data showing various surprising results, including unexpected properties possessed by the equol enantiomers, such as S-equol, that are not possessed by the racemic mixture. The results, which are discussed herein, also are being presented in the attached Rule 132 Declaration by Richard L. Jackson, PhD., and clearly support the Applicants' position that the present claims are not obvious over the art cited by the Examiner.

The data presented includes a collection of biochemical assays in which the biological activities of R-equol, S-equol, and racemic equol were evaluated and the results directly compared with each other. Specifically, each of R-equol, S-equol, and racemic equol was screened against a broad spectrum of receptor systems using standard radioligand binding assay methods adapted from the scientific literature. Reference standards were run as an integral part of each assay to ensure the validity of the results obtained. Percent inhibition results of the complete, broad spectrum of assays are reported, with the most pertinent results discussed herein.

The data clearly reflect results that are contrary to the accepted wisdom noted above, namely, that in any given system, one of the enantiomers would be the active one, the other inactive, and the racemate therefore having activity residing approximately halfway between the two. This model clearly has been shown not to be universal among the systems tested. In fact, some receptor systems yielded effects that do not fit within any model of predictability. Indeed, as the data show, in some systems, the S-enantiomer is active while the R- is not. In others, the R-enantiomer is active while the S- is not. In some systems, all three are active, and in one particular system, discussed more fully below and in the attached Declaration, both the S- and R-enantiomers are similarly active, but the racemate is inactive. It is also seen that there is even variability in activity between related receptor types.

Overall, the unusual variability in these data is, in itself, unexpected and indicative that the simple, conventional wisdom concerning the behavior of racemic mixtures in comparison to the individual enantiomers, and on which the Examiner's obviousness rejection relies, does not

apply with respect to equol. These data show that it simply would not have been obvious to prepare a successful enantiomeric or non-racemic equol composition as claimed herein, merely on the basis that racemic equol was known to exhibit some benefits.

The table below summarizes some of the more significant individual results obtained in the broad spectrum of studies, which support further the non-obviousness of enantiomeric equol compositions.

In vitro Pharmacological Screening

Target	Percent Inhibition (at 10 uM)			Interpretation (re: higher values)
	S-Equol	R-Equol	Racemate	
ERα	92	93	94	Positive control
ERβ	98	94	98	Positive control
src Protein Tyrosine Kinase LCK	27	26	1	Oncology indication
Transcription Response Factor, NF-AT	5	32	19	Anti-inflammatory indication, potential MOA
G Protein-coupled Receptor 103	58	14	38	Bone sparing, satiety, CNS effects, inflammation
Monoamine Transporter	16	51	49	CNS, antidepressant
NE Transporter	57	37	50	Antidepressant
Dopamine Transporter	84	88	92	Anti-Parkinsonism

As is clear from the above, the typical approach of simply resolving a racemate into its separate enantiomers, determining which of the two isomers is the active form (and which is the inactive form), and consequently choosing to prepare a composition using that active form,

would not be appropriate with respect to equol. One cannot reliably predict anything with respect to biological activity of the equol enantiomers, when armed only with the prior art teachings concerning the racemic mixture.

The src Protein Tyrosine Kinase (LCK) data, for example, provides a particularly interesting, and undoubtedly unexpected result. LCK is an important receptor kinase that regulates the growth of cells. When mutated, uncontrolled growth occurs. The studies here have shown that both S- and R-equol inhibit this activity approximately equally. However, racemic equol, which of course contains both R- and S-equol, surprisingly does not inhibit the activity. This is a completely unexpected finding. One simply could not have expected activity in either enantiomer, when the racemic mixture containing the two enantiomers is *inactive*. Based on these results, therefore, racemic equol would be ineffective, for example, in inhibiting cancer growth, but a composition as claimed herein, containing the S-enantiomer, would surprisingly show potential benefits. This is clear evidence of at least one unexpected property possessed by the S-enantiomer that is not possessed by the racemic mixture. In that regard, Applicants respectfully direct Examiner's attention to MPEP §716.02(a)(III), which recites that "[p]resence of a property not possessed by the prior art is evidence of nonobviousness." While this particular unexpected and surprising result is, in itself, sufficient in Applicants' view to support the present claims' nonobvious over the art's teachings with respect to racemic equol, nonobviousness of the claimed invention is also strongly supported by the totality of the evidence provided herein.

As requested by the Examiner, Applicants have presented evidence, in the form of a Rule 132 Declaration, that non-racemic equol compositions, including S-equol compositions, possess "unexpected properties not possessed by the racemic mixture." Accordingly, Applicants believe the Examiner's obviousness rejection has been fully overcome. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection set forth under 35 U.S.C. §103.

In view of the above claim amendments, remarks, and evidence presented in the attached Rule 132 Declaration, Applicants believe all of the Examiner's concerns set forth in the November 2, 2007 Office Action have been fully overcome and that the claims are in condition for allowance. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

Respectfully submitted,

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By 

Patrick T. Skacel
Attorney for Applicants
Registration No. 47,948
ROTHWELL, FIGG, ERNST & MANBECK, p.c.
1425 K Street, N.W., Suite 800
Washington, D.C. 20005
Telephone: (202)783-6040

Attachment: Rule 132 Declaration and Exhibits A-D
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